Medicine use in older adults (Part I)

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After completing this part of the module you will:

- know the accepted age of an 'elderly' or 'older adult'
- have an awareness of some statistics relating to older population and life expectancy
- understand pharmacokinetic changes that occur in older adults (in terms of absorption, distribution, metabolism and excretion)
- describe pharmacodynamic changes that occur in older adults and appreciate the relevance of this when considering drug use and potential adverse effects

Most developed countries have accepted the chronological age of 65 years as a definition of 'elderly' or 'older person'.[1] The United Kingdom (UK) population is ageing, as is the case in many other countries across the globe.[2] Indeed, the percentage of the UK population aged ≥65 years has increased from 15% in 1984 to 18% in 2014, which equates to an increase of over 3 million people.[3] In 2014, of the adults aged 65 and over, 73% were between 65 and 79 years old, 22% were between 80 and 89 years old and 5% were ≥90 years old.[3] There were over 500,000 people aged ≥90 years living in the UK in 2014, including 14,450 centenarians.[3]

According to the World Health Organization (WHO) in 2015, the average life expectancy at birth of the global population is 71.4 years.[4] Most countries in western Europe (including the UK and Ireland) and many other developed countries such as Canada, Japan, Singapore, Australia and New Zealand have a life expectancy over 80 years.[4] Moreover, a report by Public Health England (PHE) found that in England, life expectancy at older ages is now at its highest ever level. At the age of 65 years, men can be expected to live for a further 19 years and women another 21 years.[5] Improved life expectancy over recent decades is due to various factors such as advances in medical interventions, improved housing and living standards, and better nutrition. Within the next four or five years in the UK, there is a predicted increase of 12% (1.1 million) people aged >65 years [those aged >85 years will increase by 18% (300,000); and centenarians by 40% (7,000)].[6]

Increased life expectancy has an important impact on the provision of care by the National Health Service (NHS). According to a Department of Health estimate in 2010, long-term conditions account

for 70% of total health and social care spending in England, with the average cost of providing hospital and community health services for a person >85 years old about three times more than for a person who is between 65 to 74 years of age.[6] Given that the prevalence of long-term conditions increases with age,' older people are potentially living with comorbidities that are being managed with an increasing number of medicines. In England in 2015, of the almost 1.1 billion prescription items dispensed, 60.4% of the items were for patients aged 60 years and above; up from 56.9% in 2005.[7] While taking medicines has many benefits for patients, older adults are at considerable risk of experiencing negative effects from taking multiple medicines including adverse drug reactions, interactions, non-adherence, and increased hospital admissions. The remainder of this module aims to discuss the ageing process and the effects these changes can have on health and also provide guidance on medicines management.

The ageing process encompasses anatomical, physiological, psychological and sociological changes. Anatomical changes include: alteration of posture, bony hands because adipose tissue is lost from the periphery, skin becoming wrinkled and dry/dehydrated, hair thinning, greying or baldness (but new hair growth may develop in the ears of men or above the upper lip and chin in females), bone resorption, teeth being removed/lost or the enamel yellowing, nails becoming hard and thick, lean body mass decreasing and shrinking of many organs. Table 1 summarises some pertinent physiological changes. Psychological changes can be due to an organic cause or an extrinsic reason such as retirement, bereavement or loneliness. Older adults may also lose cognitive skills, including their short-term memory. Sociological factors that should be considered include a person's economic situation, where they live and their housing conditions, marital status and support systems.

Table 1 Important physiological changes in older people

Cardiovascular	Increased arterial and myocardial stiffness Increased blood pressure (typically systolic)
Gastrointestinal	Decreased gastric acid secretion Increased gastric emptying time Reduced gut motility and blood flow Reduced absorption surface/atrophy of the gastrointestinal villi
Genito-urinary	Decreased glomerular filtration rate Decrease in renal mass and renal blood flow Impaired ability to handle sodium and potassium Incomplete bladder emptying and reduced bladder capacity Decrease in the pH of vaginal secretions and in vaginal secretions
Hepatic	Reduced liver mass Reduced liver blood flow Impaired clearance of drugs that require Phase 1 metabolism
Immune	Overall function declines Increased likelihood and frequency of infections Increased prevalence of neoplasms and autoimmune disorders
Nervous	Decreased chemical transmission Decreased brain flow and impaired autoregulation of perfusion Slowed central processing and reaction time Cerebral atrophy
Respiratory	Less effective ciliary action and cough reflex is less effective Increased residual volume Decreased forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), lung mass and muscle strength

Age-related changes in pharmacokinetics (how the body handles a drug) make older people more susceptible to the effects of some medicines. Key summary points about pharmacokinetic changes are outlined in Table 2. The key pharmacokinetic parameters are summarised below:

- Absorption – most drugs are given orally and enter into the circulation from the small intestine, mostly due to its very large surface area. Absorption is affected by how lipophilic the drug molecule is, molecular size and other factors such as the pH of the surrounding environment (which affects ionisation of the drug or its stability) or the presence of food.

- Distribution – after drugs are absorbed, they are then distributed to other areas of the body through the circulation; they then move from the circulation into the tissues. The extent to which a drug stays in the circulation or moves into other compartments of the body is reflected in the Volume of Distribution (V_D). Large V_D values normally indicate the drug resides in tissues, whereas small V_D values indicate the drug has remained in the intravascular compartment.
- Metabolism – all drugs absorbed from the GI tract enter the portal circulation and pass though the liver, where so-called "first-pass metabolism" occurs. Other routes of administration avoid this initial metabolism and hence are preferable for drugs where they would be rendered inactive if taken orally, for example, glyceryl trinitrate. Metabolism, which largely occurs in the liver, has two important effects. Firstly, these 'phase one' reactions make the drug more hydrophilic, which speeds up its removal by the kidneys. Secondly, it usually (but not always) produces a metabolite that is less pharmacologically active than its parent (pro-drugs are an obvious exception to this rule, for example, enalapril).
- Excretion – most drugs and their metabolites are eliminated from the body via the kidneys. This elimination occurs by glomerular filtration or by tubular secretion at the proximal tubules by two independent carrier systems. However, many lipid-soluble drugs are reabsorbed back into the body from the renal tubules, whereas polar drugs become more concentrated in the urine as water is reabsorbed.

Table 2 The effect of ageing on drug response (age-related pharmacokinetic changes)

	Age-related changes	Clinical effects
Absorption	▪ Splanchnic and mesenteric blood flow reduced ▪ Absorptive surface reduced ▪ GI motility and gastric pH reduced	▪ The decrease in gastric emptying rate and gastro-intestinal motility tend to *delay* absorption, rather than *reduce* the amount of drug absorbed (The exception is drugs that are subject to first-pass metabolism).
Distribution	▪ Serum albumin is decreased (could be due to poor nutritional status) ▪ Total body fat increased ▪ Lean body mass and total body water decreased ▪ Age related changes in distribution/protein binding mostly of significance in the acute administration of drugs as plasma concentration at steady state is determined by clearance	▪ Higher concentrations of free drug drugs that bind to albumin) and increased therapeutic response (such as phenytoin) ▪ Longer elimination half-life of lipid soluble drugs (such as diazepam) ▪ Reduction in loading dose of water-soluble drugs required (such as digoxin)
Metabolism	▪ Liver blood flow and hepatic mass deceased ▪ Enzyme activity changes, particularly in frail older people ▪ Phase 2 metabolism is usually unaffected by ageing	▪ Decreased biotransformation and first-pass metabolism – for example, nifedipine known to have enhanced hypotensive effect due to impaired first-pass metabolism.
Excretion	▪ Renal blood flow reduced ▪ Tubular secretion/reabsorption decreased ▪ Glomerular filtration rate decreased	▪ The BNF states that "the most important effect of age is reduction in renal clearance" ▪ Decreased elimination of renally excreted drugs. Significance of reduced renal clearance depends on % of total drug eliminated by glomerular filtration/therapeutic index and may require dose reductions (such as digoxin, lithium) ▪ Acute illness can lead to rapid reduction in renal clearance – especially when accompanied by dehydration ▪ Concomitant conditions such as diabetes, heart failure and hypertension may further reduce renal function and hence lead to accumulation of drug

Pharmacodynamics (the drug's actions on a patient) can also be significantly altered with increasing age and together with the age-associated changes in pharmacokinetics, helps explain altered drug

effects. There are two types of pharmacodynamic change i.e. those due to a reduction in homeostatic reserve and those due to changes in receptors or targets[8]. Reduced homeostatic reserve relates to physiological changes in older people that mean the actions of some drugs are more likely to cause problems. Examples of where the body is less able to maintain homeostasis include the following: orthostatic responses are lessened (causing hypotension); postural control reduced (reduction in dopamine receptors in the striatum may be responsible causing an increased risk of falls); thermoregulation impaired (leading to hypothermia); cognitive function is decreased (causing confusion); and smooth muscle function declines (resulting in incontinence and constipation). Some medicines that are likely to cause problems due to these physiological changes are outlined below:

- Orthostatic responses: medicines more likely to cause hypotension include antihypertensives, tricyclics and phenothiazines. Benzodiazepines, barbiturates, morphine, levodopa and bromocriptine are known to reduce sympathetic effects via their action on the central nervous system and are therefore more likely to result in hypotension in older adults
- Postural control: medicines that increase postural sway (such as hypnotics and tranquillizers) have been associated with falls
- Thermoregulation: medicines commonly implicated in hypothermia include phenothiazines, benzodiazepines, tricyclic antidepressants and opioids.
- Cognitive function: medicines such as anticholinergics, hypnotics, H_2 antagonists and β blockers can all cause confusion.
- Smooth muscle function: a decline in gastrointestinal motility occurs with anticholinergics, opiates, tricyclics and antihistamines (making constipation or ileus more likely). Anticholinergics can cause urinary retention, especially in older men with prostatic hypertrophy. Loop diuretics may cause incontinence in patients with bladder instability or urethral dysfunction.

Responses may also be altered by changes in receptor density, affinity and post-receptor events. For example, α_2 responsiveness appears to be reduced with ageing, while α_1 remains unaffected. β adrenceptor function declines with age (decreased effects of both isoprenaline and propranolol have been noted). Changes may be due to a reduction in high-affinity binding sites or impairment of post-receptor transduction mechanisms.

Regarding the cholinergic system, effects are mostly unknown, but atropine may cause less tachycardia in older adults. Moreover, older adults are more sensitive to benzodiazepines than younger adults (mechanism unknown) meaning that lower doses should be used. Older adults are also more sensitive to warfarin (typically requiring a dose reduction) but again, the mechanism is unknown.

References

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